ClinicalEvidence

Herpes labialis

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Ching-Chi Chi

ABSTRACT

INTRODUCTION: Herpes simplex virus type 1 infection usually causes a mild, self-limiting painful blistering around the mouth, with 20% to 40% of adults affected at some time. Primary infection usually occurs in childhood, after which the virus is thought to remain latent in the trigeminal ganglion. Recurrence may be triggered by factors such as exposure to bright light, stress, and fatigue. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 42 studies. After deduplication and removal of conference abstracts, 27 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 12 studies and the further review of 15 full publications. Of the 15 full articles evaluated, one systematic review and one RCT were added at this update. We performed a GRADE evaluation for six PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information about the effectiveness and safety of oral antiviral agents, sunscreen, and topical antiviral agents.

Key points

- Herpes simplex virus type 1 infection usually causes a mild, self-limiting painful blistering around the mouth, with 20% to 40% of adults affected at some time.

  Primary infection usually occurs in childhood, after which the virus is thought to remain latent in the trigeminal ganglion.

  Recurrence may be triggered by factors such as exposure to bright light, stress, and fatigue.
- The previous version of this overview examined the evidence on treating the first attack, as well as recurrent attacks of herpes labialis. This updated version of the overview looks at interventions aimed at preventing recurrent attacks.
- We searched for evidence from RCTs and systematic reviews of RCTs in immunocompetent people.
- Many of the RCTs we found were old (the majority published between 1985 and 2004), included different regimens and different populations (with different triggers for attacks), and were of limited methodological quality.
- Prophylactic oral antiviral agents may reduce recurrent attacks compared with placebo, but we don't know the best timing and duration of treatment.

  We found evidence that oral aciclovir and oral valaciclovir may be more effective than placebo.

  However, we found no good evidence that oral famciclovir was effective, although evidence was limited to one RCT, which used artificial exposure to ultraviolet light to trigger attacks.
- We don't know whether topical antiviral agents are beneficial as prophylaxis against recurrent attacks.

  Most RCTs examined the effects of 5% topical aciclovir.
- Sunscreen may reduce recurrent attacks; however, evidence is limited.

  The evidence comes from two small crossover RCTs (57 people in total), both of which used artificial exposure to ultraviolet light to trigger attacks.

Clinical context

GENERAL BACKGROUND

Herpes labialis is a recurrent skin disease caused by re-activation of herpes simplex virus. Recurrence may be triggered by factors such as exposure to bright light, stress, and fatigue.

FOCUS OF THE REVIEW

An evidence-based review on the effects of preventative interventions is desirable. The interventions that are potentially useful in preventing herpes labialis, including oral and topical antiviral agents and sunscreens, were included in this overview.

COMMENTS ON EVIDENCE

We found one systematic review on the effects of oral antiviral agents, which included eight RCTs, and one systematic review on the effects of topical antiviral agents, which included three RCTs. We found most RCTs on the effects of oral aciclovir. We also found two RCTs on the effects of sunscreen. We found few recently published RCTs. Factors affecting the generalisability of the results to clinical practice included use of a non-proprietary preparation in one trial, regimens and included populations that varied widely between included RCTs, and, in some RCTs, use of artificial exposure to ultraviolet light to produce recurrence of lesions.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, February 2009, to November 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 42 studies. After deduplication and removal of conference abstracts, 27 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 12 studies and the further review of 15 full publications. Of the 15 full articles evaluated, one systematic review and one RCT were added at this update.

DEFINITION

Herpes labialis is a mild, self-limiting infection with herpes simplex virus type 1 (HSV-1). It causes pain and blistering on the lips and perioral area (cold sores); fever and constitutional symptoms are rare. Most people have no warning of an attack, but some experience a recognisable prodrome. In this overview, we have included studies in people with normal immunity and excluded studies in people who are immunocompromised (e.g., studies in people with HIV or with cancer undergoing chemotherapy).

INCIDENCE/ PREVALENCE

Herpes labialis accounts for about 1% of primary care consultations in the UK each year. [1] One study showed an annual prevalence of 17%, [2] while 20% to 40% of people have experienced cold sores at some time during their lifetime. [1]

AETIOLOGY/ RISK FACTORS

Herpes labialis is caused by HSV-1. After the primary infection, which usually occurs in childhood, the virus is thought to remain latent in the trigeminal ganglion. [3] A variety of factors, including exposure to bright sunlight, fatigue, psychological stress, fever, menstruation, or trauma to the area of primary infection can precipitate a recurrence. [4]

PROGNOSIS

In most people, herpes labialis is a mild, self-limiting illness. Recurrences are usually shorter and less severe than the initial attack. Healing is usually complete in 7 to 10 days without scarring. [5] Rates of re-activation are unknown. Herpes labialis can cause serious illness in immunocompromised people.

AIMS OF INTERVENTION

To reduce the frequency and severity of recurrent attacks; to speed healing of lesions; to reduce pain, with minimal adverse effects.

OUTCOMES

Rate of recurrence; **symptom improvement** (severity of symptoms and duration of symptoms; does not include time to healing or crusting of lesions); **time to healing** (time to healing/time to crusting of lesions); **quality of life**; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date November 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to November 2014, Embase 1980 to November 2014, The Cochrane Database of Systematic Reviews November 2014, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for

inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributor may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update we have removed the following previously reported questions: what are the effects of antiviral treatments for the first attack of herpes labialis? what are the effects of treatments for recurrent attacks of herpes labialis? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis?**

OPTION **PROPHYLACTIC ORAL ANTIVIRAL AGENTS VERSUS PLACEBO OR NO TREATMENT**

- For GRADE evaluation of interventions for Herpes labialis, see table, p 14 .
- Prophylactic oral antiviral agents may reduce recurrent attacks compared with placebo, but we don't know the best timing and duration of treatment.
- We found most RCT evidence on oral aciclovir.
- We found evidence showing that oral aciclovir and oral valaciclovir may be more effective than placebo at reducing the proportion of people with outbreak of lesions in those with recurrent herpes labialis.
- However, we found no good-quality evidence that oral famciclovir was effective at preventing recurrence, although evidence was limited to one RCT, which used artificial exposure to ultraviolet light to trigger attacks.

Benefits and harms

Prophylactic oral antiviral agents versus placebo:

We found one systematic review (search date 2012), [6] which included eight RCTs [7] [8] [9] [10] [11] [12] [13] [14] [15] on the use of oral antiviral agents in the prevention of recurrent herpes labialis. The review included RCTs on oral aciclovir, famciclovir, and valaciclovir only. Of the eight included RCTs, four RCTs included subjects seropositive for HSV, all participants had a history of herpes labialis, and four RCTs included people with a possible or definite sun-induced trigger. The review pooled data and reported on three outcomes: recurrence of lesions during the antiviral treatment (lesion outbreak); participant satisfaction; and adverse events. For other outcomes reported in this *BMJ Clinical Evidence* overview, such as time-to-healing, we have reported RCTs directly from their original reports.

Recurrence

Oral antiviral agents compared with placebo Prophylactic oral aciclovir and oral valaciclovir may be more effective than placebo at reducing the proportion of people with outbreak of lesions in people with recurrent herpes labialis.

However, we don't know whether oral famciclovir is more effective than placebo at reducing the outbreak of lesions in people with recurrent herpes labialis, as we found insufficient evidence from one RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[6] Systematic review	Healthy immuno-competent subjects at least 12 years of age with recurrent herpes infection 5 RCTs in this analysis	**Lesion outbreak** 44/232 (19%) with oral aciclovir 79/238 (33%) with placebo	RR 0.51 95% CI 0.29 to 0.88 P = 0.02 Significant heterogeneity in this analysis: I^2 = 64%; P for heterogeneity 0.03 See Further Information on studies	●○○	aciclovir
[6] Systematic review	Healthy immuno-competent subjects at least 12 years of age with recurrent herpes infection 2 RCTs in this analysis	**Lesion outbreak** 26/109 (24%) with oral valaciclovir 43/111 (39%) with placebo	RR 0.63 95% CI 0.43 to 0.91 P = 0.01	●○○	valaciclovir
[6] Systematic review	243 adults with a history of sun-induced recurrent herpes labialis Data from 1 RCT	**Lesion outbreak** 71/183 (39%) with oral famciclovir 31/60 (52%) with placebo The RCT used experimental exposure to ultraviolet radiation	RR 0.75 95% CI 0.55 to 1.02 P value not reported This analysis included arms with 3 different dosages of famciclovir There was no significant difference between famciclovir and placebo for each of the different dosage arms alone (125 mg; 250 mg; 500 mg) *v* placebo	⟷	Not significant

Symptom improvement

No data from the following reference on this outcome. [6]

Time-to-healing

Oral antiviral agents versus placebo Oral famciclovir may be more effective than placebo at reducing the mean time-to-healing in adults with a history of sun-induced recurrent herpes labialis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Duration of lesions** with famciclovir (500 mg) with placebo Absolute results not reported The remaining arms evaluated famciclovir (125 mg) and famciclovir (250 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reduction in healing time 2 days with famciclovir P = 0.01 for famciclovir 500 mg *v* placebo	○○○	famciclovir (500 mg)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Duration of lesions** with famciclovir (125 mg) with placebo Absolute results not reported The remaining arms evaluated famciclovir (250 mg) and famciclovir (500 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 125 mg *v* placebo	⟷	Not significant
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Duration of lesions** with famciclovir (250 mg) with placebo Absolute results not reported The remaining arms evaluated famciclovir (125 mg) and famciclovir (500 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 250 mg *v* placebo	⟷	Not significant
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Size of lesions (mean maximum area of lesion in mm²)** 55 with famciclovir (500 mg) 139 with placebo The remaining arms evaluated famciclovir (125 mg) and famciclovir (250 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	P = 0.009 for famciclovir 500 mg *v* placebo	○○○	famciclovir (500 mg)
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Size of lesions (mean maximum area of lesion in mm²)** 105 with famciclovir (125 mg) 139 with placebo The remaining arms evaluated famciclovir (250 mg) and famciclovir (500 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	P = 0.38 for famciclovir 125 mg *v* placebo	⟷	Not significant
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Size of lesions (mean maximum area of lesion in mm²)** 77 with famciclovir (250 mg) 139 with placebo The remaining arms evaluated famciclovir (125 mg) and famciclovir (500 mg) Treatment was given 3 times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	P = 0.09 for famciclovir 250 mg *v* placebo	⟷	Not significant

No data from the following reference on this outcome. [6]

Quality of life

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] RCT	147 US skiers with a history of herpes labialis precipitated by ultraviolet light In review [6]	**Mild to moderate central nervous system or gastrointestinal tract adverse events** 7/77 (9%) with aciclovir (400 mg twice daily, starting 12 hours before ultraviolet exposure) 3/76 (4%) with placebo	P = 0.34	⟷	Not significant
[9] RCT	239 Canadian skiers with a history of recurrent herpes labialis In review [6]	**Rates of adverse events** 58/115 (50%) with aciclovir (800 mg twice daily) 59/124 (48%) with placebo Headache and nausea were the most common adverse effects reported Aciclovir was started on the day before exposure to ultraviolet light for a minimum of 3 days to a maximum of 7 days All participants were allowed to use paracetamol (acetaminophen) and encouraged to use sunscreen	P = 0.68	⟷	Not significant
[9] RCT	239 Canadian skiers with a history of recurrent herpes labialis In review [6]	**Number of severe adverse events** 5 with aciclovir (800 mg twice daily) 6 with placebo Severe adverse effects associated with aciclovir were knee throbbing, constipation, cold sore discomfort, stomach ache, and depression Severe adverse effects associated with placebo were insomnia, diarrhoea, and headache (4 people) Aciclovir was started on the day before exposure to ultraviolet light for a minimum of 3 days to a maximum of 7 days All participants were allowed to use paracetamol (acetaminophen) and encouraged to use sunscreen			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Headache or nausea (most common adverse events)** with famciclovir (125 mg) with famciclovir (250 mg) with famciclovir (500 mg) with placebo Absolute results not reported	Difference among groups reported as not significant (between-group differences not assessed) P value not reported	⟷	Not significant
[12] RCT **4-armed trial**	243 adults with a history of sun-induced recurrent herpes labialis In review [6]	**Severe adverse events, within 30 days of the last dose of famciclovir** with famciclovir (125 mg) with famciclovir (250 mg) with famciclovir (500 mg) with placebo Absolute results not reported The analysis reported that no severe adverse events occurred in any group			
[11] pooled analysis of 2 RCTs	98 adults with a history of 4 or more attacks in the previous year In review [6]	**Adverse events** 22 events in 33% of people with valaciclovir 29 events in 39% of people with placebo Most common adverse effect reported was mild headache None of the adverse events in the valaciclovir group and only 3 in the placebo group were reported to be treatment related			

Further information on studies

[6] *Methods* Of the eight included RCTs, seven RCTs had unclear risk of bias for adequate sequence generation, five had unclear risk for allocation concealment, and three were at high risk for incomplete outcome data. The review reported that, overall, three RCTs were at high risk of bias. The review noted that the regimens used varied between studies, the trials differed when the antiviral drugs were taken by participants (e.g., for valaciclovir, daily for 4 months in one trial, and over 2 days in another), and the different protocols may have influenced the results. It also noted that people were exposed to different triggers (e.g., sun exposure and dental treatment), and in two RCTs the trigger was artificial (experimental) exposure to ultraviolet radiation. Included trials were published between 1985 and 2004. The review reported that the findings from the review should be interpreted with caution because of these methodological limitations.

[6] The review also presented a pooled analysis for all antiviral RCTs (including oral and topical agents, all different antiviral agents) versus placebo and found a significant difference favouring the antiviral agents (10 RCTs, 1250 people, RR 0.70, 95% CI 0.55 to 0.89; P = 0.003). However, the combined studies also produced significant heterogeneity (I^2 = 61%; P = 0.004). Significant heterogeneity was also found when comparing oral aciclovir alone versus placebo, potentially because of the differences between dosages across the various studies.

Comment: The interpretation and applicability of the results are limited by the heterogeneity in the regimens, study protocols, and baseline risk of herpes labialis.

Clinical guide
Oral antivirals may be effective in reducing recurrences of herpes labialis.

OPTION PROPHYLACTIC TOPICAL ANTIVIRAL AGENTS VERSUS PLACEBO OR NO TREATMENT

- For GRADE evaluation of interventions for Herpes labialis, see table, p 14 .
- We don't know whether topical antiviral treatments are beneficial as prophylaxis against recurrent attacks.
- We found four RCTs, three of which examined the effects of 5% aciclovir cream.
- The other trial examined the effects of a non-proprietary agent, and we were unable to draw robust conclusions from this RCT.

Benefits and harms

Topical antiviral agents versus placebo:

We found one systematic review (search date 2012), [6] which included three RCTs [13] [16] [17] on the use of topical antiviral agents in the prevention of recurrent herpes labialis. The review only included studies of 5% aciclovir cream. All participants had recurrent herpes labialis, two RCTs included people with sun-triggered lesions, and one RCT included HSV seropositive subjects. The RCTs were published between 1986 and 1991. The review pooled data and reported on three outcomes: recurrence of lesions during the antiviral treatment (lesion outbreak); participant satisfaction; and adverse effects. For other outcomes reported in this *BMJ Clinical Evidence* overview, such as time to healing and symptom improvement, we have reported RCTs directly from their original reports. We also found one subsequent RCT, which compared a non-proprietary gel versus placebo (see Further information on studies). [18]

Recurrence

Topical antivirals compared with placebo We don't know whether prophylactic 5% aciclovir cream is more effective than placebo cream at reducing the outbreak of lesions in people with recurrent herpes labialis. A non-proprietary topical gel (containing 2-hydroxypropyl-ß-cyclodextrin) may be less effective than placebo at reducing relapses in people with recurrent herpes labialis, but evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[6] Systematic review	Healthy immuno-competent subjects at least 12 years of age with recurrent herpes infection 3 RCTs in this analysis	**Lesion outbreak** 57/159 (36%) with 5% aciclovir cream 63/158 (40%) with placebo	RR 0.92 95% CI 0.71 to 1.19 P = 0.52	⟷	Not significant
[18] RCT	40 people aged 18–50 years with a history of 8 or more herpes labialis relapses in the previous year	**Herpes labialis relapses** with topical gel with placebo Absolute results not reported 33 people in this analysis	P = 0.003 The RCT found a significantly higher number of relapses in the topical gel group	○○○	placebo

Symptom improvement

Topical antivirals compared with placebo We don't know whether prophylactic 5% aciclovir cream is more effective than placebo cream at reducing the duration of pain in people with herpes labialis precipitated by exposure to sunlight. We don't know whether a non-proprietary topical gel (containing 2-hydroxypropyl-beta-cyclodextrin) is more effective than placebo at reducing symptoms, as we found insufficient evidence from one RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[13] RCT **4-armed trial**	196 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight	**Mean duration of pain** 3.7 days with 5% aciclovir cream 3.6 days with placebo cream 90 people in this analysis	P >0.10 Results should be interpreted with care, as the RCT was conducted under artificial conditions	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [6]	Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure The remaining arms evaluated aciclovir capsules and placebo capsules			
[18] RCT	40 people aged 18–50 years with a history of 8 or more herpes labialis relapses in the previous year	**Total symptom severity score (intensity of different prodromal signs, not further defined)** with topical gel with placebo Absolute results not reported Unclear how many participants in this analysis	P = 0.048 Result of borderline significance The RCT reported that individual symptom severity scores were significantly higher with placebo for tingling and burning but not for tension, hypersensitivity, or itching	○○○	topical gel

Time-to-healing

Topical antivirals compared with placebo We don't know whether prophylactic aciclovir cream is more effective than placebo cream at reducing mean healing time in people with herpes labialis precipitated by exposure to sunlight (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[13] RCT **4-armed trial**	196 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [6]	**Mean healing time to loss of crust** 6.7 days with 5% aciclovir cream 6.5 days with placebo cream 90 people in this analysis Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure The remaining arms evaluated aciclovir capsules and placebo capsules	P = 0.79 Results should be interpreted with care, as the RCT was conducted under artificial conditions	⟷	Not significant
[13] RCT **4-armed trial**	196 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [6]	**Mean healing time to normal skin** 6.8 days with 5% aciclovir cream 7.4 days with placebo cream 90 people in this analysis Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure The remaining arms evaluated aciclovir capsules and placebo capsules	P = 0.70 Results should be interpreted with care, as the RCT was conducted under artificial conditions	⟷	Not significant

No data from the following reference on this outcome. [18]

Quality of life

No data from the following reference on this outcome. [6] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT	196 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [6]	**Adverse effects** with aciclovir cream with placebo cream Absolute results not reported 90 people in this analysis No local or systemic adverse reactions to treatment reported			
[17] RCT	196 skiers aged 18 years or older, with 3 episodes of sun-induced herpes labialis during the previous year In review [6]	**People reporting at least one adverse effect (not further defined)** 15/95 (16%) with aciclovir cream 13/96 (14%) with placebo cream	Reported as not significant P value not reported	⟷	Not significant
[18] RCT	40 people aged 18–50 years, with a history of 8 or more herpes labialis relapses in the previous year	**Adverse events** 128 with topical gel 117 with placebo The RCT reported that the most frequent adverse events were itching, tickling, burning, dry lips, and erythema	P value not reported		

Further information on studies

[6] *Methods* Of the three included RCTs, all had unclear risk of bias for adequate sequence generation, two had unclear risk of bias for allocation concealment, and two had unclear risk for incomplete outcome data. One RCT was at high risk for incomplete outcome data, and one RCT was reported to be at high risk of bias overall. One RCT used artificial (experimental) ultraviolet light as a trigger. All used 5% aciclovir cream, one RCT over 32 weeks, one RCT 12 hours before sun exposure to a maximum of 7 days, and one RCT for 7 days prior to artificial ultraviolet light exposure. The review also performed an analysis for all antiviral agents (topical and oral) versus placebo (see Prophylactic oral antiviral agents versus placebo or no treatment, p 3).

[18] This double-blind RCT (40 immunocompetent adults, 18–50 years, at least 8 herpes labialis relapses in the previous year) compared a topical gel (composed of 20% 2-hydroxypropyl-beta-cyclodextrin [2-HPBCD] dissolved in various polyethylene glycols [PEGs]) with placebo (a mixture of the same PEGs) applied to lips twice daily for 6 months. The study did not report methods of allocation concealment, randomisation, or blinding. The study drug was provided by the pharmaceutical company that sponsored the study. The RCT reported that both groups had significantly fewer recurrences during study treatment compared to the time before the study (baseline analysis), which led it to suggest the possibility that the PEG component in both groups may have had some effect. However, this was speculative, and this RCT was not designed to test this hypothesis.

Comment: The available evidence does not support the efficacy of topical antivirals in preventing herpes labialis.

Clinical guide
Topical antivirals are unlikely to benefit in reducing the frequency of herpes labialis.

OPTION PROPHYLACTIC SUNSCREEN VERSUS PLACEBO OR NO TREATMENT

- For GRADE evaluation of interventions for Herpes labialis, see table, p 14 .
- Sunscreen may reduce recurrent attacks; however, evidence is limited.
- We found two RCTs (57 people in total) on the effects of sunscreen.
- However, both RCTs used artificial exposure to ultraviolet light to trigger attacks.
- The preventative effects of sunscreen under natural sunlight exposure may be different.

Benefits and harms

Sunscreen versus placebo:

We found one systematic review (search date 2008), [7] including one RCT of sufficient quality. [19] We found one additional RCT. [20] We have reported the RCTs directly from their original reports. The RCTs were published in 1991 and 1998.

Recurrence

Sunscreen compared with placebo Sunscreen may be more effective than placebo at decreasing the proportion of people with recurrence at 6 days. However, evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[19] RCT **Crossover design**	38 people with a history of recurrent herpes In review [7]	**Recurrence , at 6 days** 0/35 (0%) with sunscreen 27/38 (71%) with placebo Post-crossover results	P <0.001 Results should be interpreted with caution as crossover designs have important limitations	○○○	sunscreen
[20] RCT **Crossover design**	19 people exposed to a pre-established dose of ultraviolet light in a laboratory	**Recurrence , at 6 days** 1/19 (5%) with sunscreen 11/19 (58%) with placebo Post-crossover results	P <0.01 Results should be interpreted with caution as crossover designs have important limitations and the RCT was conducted under artificial conditions	○○○	sunscreen

Symptom improvement

No data from the following reference on this outcome. [19] [20]

Time-to-healing

No data from the following reference on this outcome. [19] [20]

Quality of life

No data from the following reference on this outcome. [19] [20]

Adverse effects

No data from the following reference on this outcome. [19] [20]

Further information on studies

[19] This double-blind crossover RCT included 38 adults aged 18 to 60 years with a history of recurrent herpes labialis at least once per year, and who were seropositive for HSV. In total, 22/38 (58%) of participants stated that sun exposure was a predisposing factor in recurrence. People were randomised using a coin-based method to either a commercially available sunscreen or placebo prior to receiving ultraviolet light. Three days after exposure, participants and investigators were asked to guess which treatment was given. Partial un-blinding happened (80% identified placebo) because erythema developed after exposures to ultraviolet light on placebo. The results of this study should be interpreted with caution since people were exposed to artificial ultraviolet light to induce recurrence, and due to the limitations of a crossover design.

[20] This crossover RCT included 19 adults aged 19 to 48 years with at least two herpes labialis recurrences per year. Washout period was 4 weeks. The RCT compared a sunblock stick with a vehicle stick with no sunlight-absorbing filters. People were exposed to ultraviolet light to induce recurrence. Each participant had previously been tested to determine a minimal erythema dose to induce a perceptible erythema on the forearm. The results of this study should be interpreted with caution since people were exposed to artificial ultraviolet light, and due to the limitations of a crossover design.

Comment: Experiments using artificial ultraviolet light showed sunscreen to be effective in preventing herpes labialis, but the effects of sunscreen in preventing herpes labialis under natural sunlight exposure may differ. In addition to the condition under which sunscreen is used, other factors including the compositions and formulations of sunscreen, the thickness, and frequency of applying sunscreen may affect the effects of sunscreen.

Clinical guide
Sunscreen might be helpful in reducing recurrences of herpes labialis. However, the evidence is limited and various factors may affect the effects of sunscreen.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Prophylactic oral antiviral agents versus placebo or no treatment One systematic review added. [6] Categorisation unchanged (likely to be beneficial).

Prophylactic topical antiviral agents versus placebo or no treatment One systematic review [6] and one subsequent RCT [18] added. Categorisation unchanged (unknown effectiveness).

Prophylactic sunscreen versus placebo or no treatment Existing evidence re-evaluated. Categorisation unchanged (likely to be beneficial).

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Ching-Chi Chi
Director and Professor
Department of Dermatology
Chang Gung Memorial Hospital, College of Medicine, Chang Gung University
Puzih, Chiayi
Taiwan

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Disclaimer

GRADE **Evaluation of interventions for Herpes labialis.**

Important outcomes			Quality of life, Recurrence, Symptom improvement , Time-to-healing						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis?									
8 (933) [6]	Recurrence	Prophylactic oral antiviral agents versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for significant statistical heterogeneity; directness point deducted for experimental exposure to artificial ultraviolet light and differences between RCT affecting generalisability (triggers used, regimens used)
1 (243) [12]	Time-to-healing	Prophylactic oral antiviral agents versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and use of experimental exposure to artificial ultraviolet light
4 (350) [6] [18]	Recurrence	Topical antiviral agents versus placebo	4	–2	0	–2	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness points deducted for experimental exposure to artificial ultraviolet light, different regimens between different RCTs, and use of a non-proprietary preparation
2 (at least 90) [13] [18]	Symptom improvement	Topical antiviral agents versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for weak methods, sparse data, and incomplete reporting of results; directness point deducted for experimental exposure to artificial ultraviolet light
1 (90) [13]	Time-to-healing	Topical antiviral agents versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for experimental exposure to artificial ultraviolet light
2 (57) [19] [20]	Recurrence	Sunscreen versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and short follow-up; directness point deducted for use of experimental exposure to artificial ultraviolet light

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.